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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/901,612	07/28/97	FRANK B	HYZ-041FWC

HM12/1023

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EXAMINER	
LARSON, T	
ART UNIT	**PAPER NUMBER**
1635	35

DATE MAILED: 10/23/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/901,612	FRANK ET AL.	
	Examiner	Art Unit	
	Thomas G. Larson, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *03 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-20,36,40-50 and 207-225* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *17,19 and 211-224* is/are allowed.

6)☒ Claim(s) *1,8-20,36,40-50 and 225* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

1. The request filed on 8/3/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/901,612 is acceptable and a CPA has been established. An action on the CPA follows.

2. The disclosure is objected to because of the following informalities:

The specification at p. 29, ln. 2, indicates that oligonucleotide HBV6 has the sequence set forth in SEQ. ID. NO: 32, but Table 1, p. 16, shows that HBV6 has the sequence set forth in SEQ. ID. NO: 45. Note that Table 2 teaches that it is HBV-19 that has the sequence set forth in SEQ. ID. NO: 32.

Appropriate correction is required.

3. The rejection of claims 1, 8-20, 36, 40-50, and 207-225 under 35 U.S.C. 112, first paragraph, is with drawn in view of the interview 8/21/00 and the newly found art made of record below.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1, 40-46 and 50 are rejected under 35 U.S.C. 102(e) as being anticipated by Korba et al. (US Patent No. 5,646,262).

Claim 1 is drawn to an antisense oligonucleotide complementary to a portion of the HBV epsilon region and which inhibits HBV replication. Claims 40-43 limit claim 1 to the oligonucleotide comprising various modifications including phosphorothioate and alkyl phosphonate linkages. Claims 44-46 limit the oligonucleotide of claim 1 to comprising ribonucleotides and/or deoxyribonucleotides. Claim 50 is drawn to a pharmaceutical composition comprising the antisense oligonucleotide of claim 1.

Korba et al. teach oligonucleotides antisense to the epsilon region of HBV and which inhibit HBV replication (abstract, Figure 4, and Table 1). Korba teaches that these oligonucleotides may be base on ribonucleotides or deoxyribonucleotides . Korba et al. further teach that the oligos may be modified and discloses phosphodiester, phosphorothioate or methylphosphonate linkages as examples of modifications (col. 6, ln. 61, - col. 7, ln. 13). Korba et al. teach pharmaceutical compositions comprising oligonucleotides (col. 9, ln. 1, -col. 10, ln. 46).

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 8-14 , 36, 48 49 and 225 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korba et al. (US Patent No. 5,646,262).

Claims 1, 8-14, 36 and 225 are drawn to oligonucleotides "comprising" or ("having" in the case of claim 225) the sequences set forth in SEQ. ID. NOS: 7-13 and 45. Note the use of the open transitional language "comprising" and "having". Note also that these oligonucleotides are targeted to a region consisting of nucleotide positions 1828-1895 of HBV, as set forth in Table 1, p. 16 of the specification). Claims 48 and 49 are drawn to kits comprising one or more oligonucleotides of claim 1.

Korba et al. teach a large number of different oligonucleotides directed to the region consisting of nucleotides 1841 to 1908 of the HBV genome (oligonucleotide L1e starts at 1841 while L2d starts at 1887 (col. 13, lns. 22-39) to end at 1908). These oligonucleotides have various lengths and exhibit various levels of activity (Fig. 4 and Table 1) with respect to reducing levels of HBV. Korba et al. do not teach antisense oligonucleotides comprising the specific subsequences within the 1841 to 1908 target region set forth in the claims. Korba et al. also do not teach a kit comprising one or more oligonucleotide of claim 1.

It would have been obvious to the artisan of ordinary skill to develop additional oligonucleotides to the 1841 to 1908 target region of HBV. Because the target region is small (67 nucleotides) relative to the size of the sequences claimed

(generally about 20 nucleotides) and Korba et al. provide general guidance that oligonucleotide length is preferred to be 14 to 25 nucleotides in length, the artisan would have at once envisaged oligonucleotides comprising the claimed sequences for testing. One would have been motivated to do so as a matter of routine experimentation to determine optimized antisense oligonucleotide sequences targeting this region. One would have had a reasonable expectation of success because Korba et al. clearly show that oligonucleotides targeted to different subsequences within the target region have different levels of activity with some being more active than others (Fig. 4).

Regarding the kit claims, it would have been further obvious to prepare the oligonucleotides for testing in the form of a kit to provide the benefits of convenience to the experimenter and to insure reproducibility by providing the oligonucleotide in a uniform format.

8. Claims 1, 8-15, 16, 18, 20, 36, 48, 49 and 225 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korba et al. as applied to claims 1, 8-14 , 36, 48 49 and 225 above, and further in view of Wu et al. (cited in the Office action mailed 5/28/96) or Wu et al. (designated B4 on the PTO-1449 submitted with the information disclosure statement filed 8/24/95).

Claims 1, 15, 16, 18, 20 and 225 are drawn to oligonucleotides "comprising" or ("having" in the case of claim 225) the sequences set forth in SEQ. ID. NOS: 14, 15,

17, and 19. Note the use of the open transitional language "comprising" and "having". Note also that these oligonucleotides are targeted to a region consisting of nucleotide positions 1894-1929 of HBV, as set forth in Table 1, p. 16 of the specification). Claims 8-14, 36, 48 and 49 are drawn as set forth above.

Korba et al. is applied as above.

Both Wu et al. documents teach an oligonucleotide targeted to nucleotides 1903-1923 of HBV (Wu et al. (J. Biol. Chem.) p. 12436, col. 2, 2nd full ¶, lns. 11-15; Wu et al. (WO 93/04701), p. 10, ln. 8). Wu et al teach that this oligonucleotide produces a reduction in HBV surface antigen (Wu et al. (J. Biol. Chem.) abstract, lns 9-14; Wu et al. (WO 93/04701), Fig. 2). Neither Wu et al. document teaches an oligonucleotide comprising SEQ. ID. NOS: 14, 15, 17, or 19.

It would have been obvious to the artisan of ordinary skill to combine the teachings of the Korba reference with those of either Wu et al. reference to extend the HBV antisense target region from the region bounded by nucleotides 1841 to 1908, to that bounded by nucleotides 1841 to at least 1923. One would have been motivated to do so to find additional optimized antisense oligonucleotides for inhibiting HBV, more particularly those that can reduce HBV antigen levels. As noted above, because the target region is small (82 nucleotides) relative to the size of the sequences claimed (generally about 20 nucleotides) and Korba et al. provide general guidance that oligonucleotide length is preferred to be 14 to 25 nucleotides in length, the artisan would have at once envisaged oligonucleotides comprising the

claimed sequences for testing. One would have had a reasonable expectation of success because Korba et al. show that antisense oligonucleotides targeted to the region approaching nucleotide 1908 begin to reduce HBC antigen levels (Fig. 4, oligos L2b-L2e).

9. Claims 17, 19 and 211-224 are free of the art searched and of record. Base claims 17 and 19 are respectively drawn to oligonucleotides consisting of the sequences set forth in SEQ. ID. NOS: 16 and 18. Although these oligonucleotides are targeted to the same region of the HBV genome as the oligonucleotide disclosed by Wu et al. and Wu et al (WO93/04701, SEQ. ID. NO: 1) (see office actions mailed 5/28/96 and 11/29/96), they are distinct from the oligonucleotide disclosed in both Wu et al. documents because they are shorter. Wu discloses nothing that would suggest or make obvious the specific oligonucleotide sequences set forth in SEQ. ID. NOS: 16 and 18.

10. Claims 1, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korba et al. in view of Uhlmann et al. (cited in the Office action mailed 5/28/96.

The claims are drawn to an antisense oligonucleotide complementary to a portion of the HBV epsilon region and which inhibits HBV replication and which comprises at least one ribonucleotide and at least one 2'-O-methyl nucleotide.

Korba et al. teach oligonucleotides antisense to the epsilon region of HBV and which inhibit HBV replication (abstract, Figure 4, and Table 1). Korba teaches that these oligonucleotides may be base on ribonucleotides and may be modified (col. 6, ln. 61, - col. 7, ln. 13). Korba et al. do not specifically disclose a 2'-O-methyl modification.

Uhlmann et al. describe the 2'-O-methyl modification of oligodeoxyribonucleotides and teaches that the modification confers the advantages of increased oligonucleotide stability and increased thermal stability of the oligonucleotide-target mRNA complex (p. 558, ¶ bridging cols. 1 and 2). Uhlmann does not teach an antisense oligonucleotide targeted to HBV.

It would have been obvious to the artisan of ordinary skill to combine the teachings of Korba et al. and Uhlmann et al. to produce antisense oligonucleotides targeted to the epsilon region of HBV and comprising 2'-O-methyl ribonucleotides. One would have been motivated to do so to increase the stability and target affinity of the oligonucleotides taught by Korba et al. One would have had a reasonable expectation of success because Uhlmann specifically teaches that incorporation of 2'-O-methyl ribonucleotides into antisense oligonucleotides is known to provide the oligos with these properties.

11. No claim is allowed.

12. Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The FAX numbers are (703) 308-4242 and (703) 308-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Unofficial papers, such as draft responses, may be transmitted to the examiner directly at (703) 305-7939. It is recommended that the examiner be notified when a fax is sent to this number.

Any inquiry concerning this communication or earlier communications should be directed to Thom Larson, whose telephone number is (703) 308-7309. The examiner normally can be reached Monday through Friday from 9:00 AM to 5:30 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

Thomas G. Larson, Ph.D.
Examiner